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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/678,947

10/03/2003

Martin Quibell

1718-0208P

1147

2292

7590

05/01/2006

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EXAMINER

YOUNG, SHAWQUIA

ART UNIT

PAPER NUMBER

1626

DATE MAILED: 05/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/678,947	Applicant(s) QUIBELL ET AL.	
	Examiner Shawquia Young	Art Unit 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) 15-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-14 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>10/3/2003</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Claims 1-20 are currently pending in the instant application.

I. *Priority*

The instant application is a Divisional of US Application 10/042,565, filed on November 16, 2001, which was abandoned, which in turn is a Continuation In Part of US Application 10/015,186, filed on November 16, 2001, which was abandoned, which in turn is a Continuation In Part of International Application PCT/GB00/01894, filed on May 18, 2000 and claims benefit of US Provisional Applications 60/252,802, filed on November 17, 2000 and 60/252, 840, filed on November 17, 2000.

II. *Information Disclosure Statement*

The information disclosure statement (IDS) submitted on October 3, 2003 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

III. *Restriction/Election*

A. *Election: Applicant's Response*

Applicants' election with traverse of Group I, and the species of benzofuran-2-carboxylic acid (3-methyl-1S-(2R-methyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-butyl)amide, in the reply filed on April 4, 2006 is acknowledged. The traversal is on the ground (s) that the point at which the scope of the restriction group becomes final is unreasonable, being that it unfairly removes Applicants' rights to argue

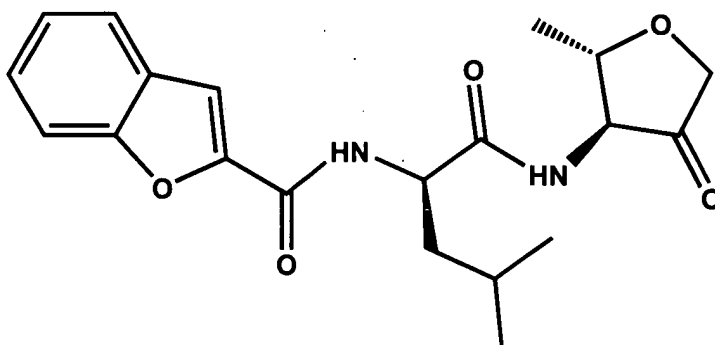
Art Unit: 1626

against the restriction because it is unclear what is encompassed by the scope of the restriction group. However as mentioned earlier, the restriction requirement will not be made final (page 4, lines 7-10 of Office Action, Requirement of Restriction) and the applicant has the right to argue against the restriction.

Subject matter not encompassed by elected Group I are withdrawn from further consideration pursuant to 37 CFR 1.142 (b), as being drawn to nonelected inventions.

B. Status of the Claims

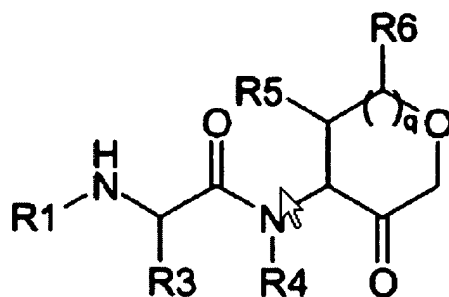
i. Scope of the Elected Subject Matter



benzofuran-2carboxylic acid (3 methyl-1S-(2R-methyl-4-oxo-tetrahydrofuran-3S-ylcarbamoyl)-butyl)amide

The above structure is the provisional elected species. Thus the scope of the subject matter is the compounds of formula (IV) in claims 1-14 wherein:

Art Unit: 1626



R1 is $R'C(O)$, $R'SO_2$;

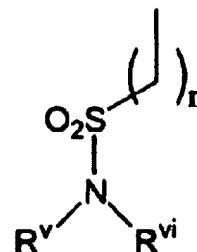
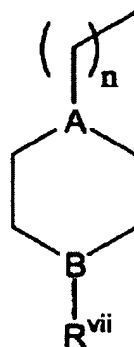
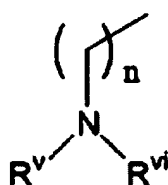
R' is a bicyclic, saturated or unsaturated, 8-12 membered ring system containing 0-4 hetero atoms selected from S and O, which is optionally substituted with up to four substituents independently selected from groups as recited in claim 1;

R3 is C_1 - C_7 alkyl, C_2 - C_7 alkenyl, phenyl- C_1 - C_7 alkyl, furanyl- C_1 - C_7 alkyl, thienyl- C_1 - C_7 alkyl, phenyl, furanyl, thienyl, C_3 - C_7 cycloalkyl;

R4 is H, C_1 - C_7 alkyl, phenyl- C_1 - C_7 alkyl, furanyl- C_1 - C_7 alkyl, thienyl- C_1 - C_7 alkyl, phenyl, furanyl, thienyl, C_3 - C_7 cycloalkyl, or C_2 - C_7 alkenyl;

R5 is C_1 - C_7 alkyl, halogen, phenyl- C_1 - C_7 alkyl, furanyl- C_1 - C_7 alkyl, thienyl- C_1 - C_7 alkyl, C_0 - C_3 -alkyl-CONR³R⁴ or R^{iv}

Art Unit: 1626

 R^{iv} iswhere $n = 1-3$; R^v , R^{vi} is H, C_1-C_7 alkyl;**A** is CH; **B** is O, S, CH; R^{vii} is absent when **B** is O, S; R^{vii} is H, C_1-C_7 alkyl when **B** is CH; q is 0;ii. Extended Prior Art Search M.P.E.P. §803.02

If upon examination of the elected species, no prior art is found that would anticipate or render obvious the instant invention based on the elected species, the search of the Markush-type claim will be extended.

See M.P.E.P. § 803.02 (2001). If prior art is then found that anticipates or renders obvious the non-elected species, the Markush-type claim will be rejected. It should be noted that the prior art search will not be extended unnecessarily to cover all non-elected species. Should Applicant overcome the rejection by amending the claim, the amended claim will be reexamined. Id. The prior art search will be extended to the extent

necessary to determine patentability of the Markush-type claim. Id. In the event prior art is found during reexamination that renders obvious or anticipates the amended Markush-type claim, the claim will be rejected and the action made final. Id.

As indicated above, Examiner searched the compound based on the elected species, above, in response to the requirement to restrict the products of Formula (IV), wherein: there was prior art of record (WO 98/50533) that anticipated or rendered obvious the elected species and therefore the scope of the subject matter was **not extended or broaden** in pursuant to M.P.E.P. § 803.02.

iii. Non-elected Subject Matter Withdrawn 37 C.F.R. §1.142(b)

The non-elected subject matter withdrawn are the compounds of formula (IV), claims 1-4, 6-14 (in-part) and 5 (as a whole) wherein:

R1 is $R'C(O)$, $R'SO_2$;

R' is a bicyclic, saturated or unsaturated, 8-12 membered ring system containing 0-4 hetero atoms selected from S, O, and N, which is optionally substituted with up to four substituents independently selected from groups as recited in claim 1;

R3 is pyrazolyl- C_1-C_7 alkyl, pyridyl- C_1-C_7 alkyl, imidazolyl- C_1-C_7 alkyl, oxazolyl- C_1-C_7 alkyl, isoxazolyl- C_1-C_7 alkyl, thiazinyl- C_1-C_7 alkyl, isothiazinyl- C_1-C_7 alkyl, thiazolyl- C_1-C_7 alkyl, oxadiazolyl- C_1-C_7 alkyl, 1,2,3-triazolyl- C_1-C_7 alkyl, 1,2,4-triazolyl- C_1-C_7 alkyl, pyrazolyl, pyridyl,

Art Unit: 1626

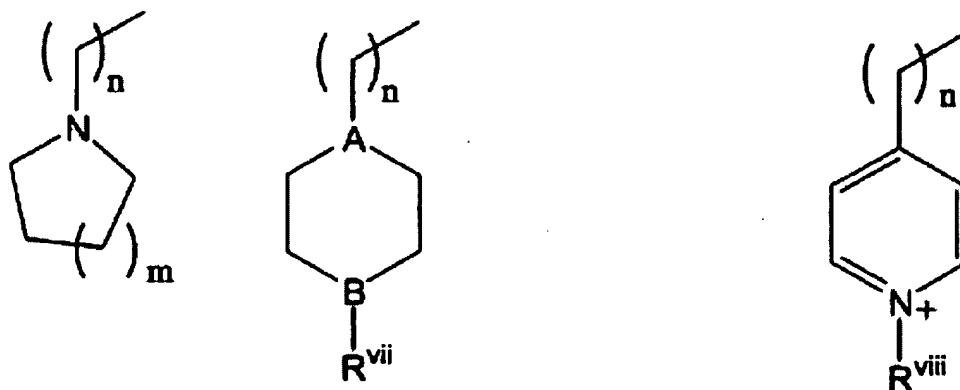
imidazolyl, oxazolyl, isoxazolyl, thiazinyl, isothiazinyl, thiazolyl,
oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl;

R₄ is pyrazolyl-C₁-C₇ alkyl, pyridyl-C₁-C₇ alkyl, imidazolyl-C₁-C₇ alkyl,
oxazolyl-C₁-C₇ alkyl, isoxazolyl-C₁-C₇ alkyl, thiazinyl-C₁-C₇ alkyl,
isothiazinyl-C₁-C₇ alkyl, thiazolyl-C₁-C₇ alkyl, oxadiazolyl-C₁-C₇ alkyl,
1,2,3-triazolyl-C₁-C₇ alkyl, 1,2,4-triazolyl-C₁-C₇ alkyl, pyrazolyl, pyridyl,
imidazolyl, oxazolyl, isoxazolyl, thiazinyl, isothiazinyl, thiazolyl,
oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl;

R₅ is pyrazolyl-C₁-C₇ alkyl, pyridyl-C₁-C₇ alkyl, imidazolyl-C₁-C₇ alkyl,
oxazolyl-C₁-C₇ alkyl, isoxazolyl-C₁-C₇ alkyl, thiazinyl-C₁-C₇ alkyl,
isothiazinyl-C₁-C₇ alkyl, thiazolyl-C₁-C₇ alkyl, oxadiazolyl-C₁-C₇ alkyl,
1,2,3-triazolyl-C₁-C₇ alkyl, 1,2,4-triazolyl-C₁-C₇ alkyl, C₀-C₃-alkyl-

CONR₃R₄ or R^{iv}

R^{iv} is



where **n** = 1-3, **m** = 1-3;

A is N, CH; **B** is N, O, S, CH;

Art Unit: 1626

R^{vii} is H, C₁-C₇ alkyl when **B** is N;

R^{viii} is O, C₁-C₇ alkyl; H, C₁-C₇ alkyl, Ar-C₁-C₇ alkyl, C₁-C₃-alkyl-C(O)-

NHR^{ix}, C₁-C₃-alkyl-SO₂-NHR^{ix}, CH₂Xphenyl, CH₂Xthienyl, CH₂Xfuranyl;

R^{ix} is C₁-C₇ alkyl, C₁-C₇ alkyl phenyl-C₁-C₇ alkyl, furanyl-C₁-C₇ alkyl,

thienyl-C₁-C₇ alkyl, C₃-C₆ cycloalkyl

q is 0 or 1;

IV. Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite.

In claim 1, there is no definition provided for the R6 variable. It is unclear what exactly R6 encompasses in the claimed invention.

35 USC § 103 - OBVIOUSNESS REJECTION

The following is a quotation of 35 U.S.C. § 103(a) that forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

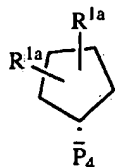
Graham v. John Deere Co. set forth the factual inquiries necessary to determine obviousness under 35 U.S.C. §103(a). See *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Specifically, the analysis must employ the following factual inquiries:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *Gribble, et al.*, WO 98/50533 (May. 6, 1998).

Applicants claim cysteine protease inhibitors of the formula (IV), defined in claim 1. The provisionally elected species is benzofuran-2carboxylic acid (3 methyl-1S-(2R-methyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-butyl)amide.

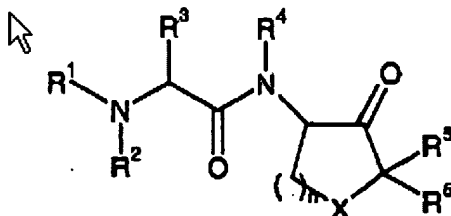
The Scope and Content of the Prior Art (MPEP §2141.01)



et al. teaches compounds of the formula (I) that inhibit cysteine

particularly cathepsin K. (*Gribble, et al.*, p. 3, lines 8-13). The invention

by the general formula (I):



wherein R^1 is R'' , $R''C(O)$, $R''C(S)$, $R''SO_2$, $R''OC(O)$, $R''R'NC(O)$, or $R''OC(O)NR'CH(R^6)C(O)$ (*Gribble, et al.*, p. 4, lines 7-8); R^2 is H, C_{1-6} alkyl, C_{2-6} alkenyl, Ar- C_{0-6} alkyl, or Het- C_{0-6} alkyl (*Gribble, et al.*, p. 4, line 9); R^3 are H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl- C_{0-6} alkyl, Ar- C_{0-6} alkyl, or Het- C_{0-6} alkyl (*Gribble, et al.*, p. 4, lines 10-11); R^4 is H, C_{1-6} alkyl, C_{2-6} alkenyl, Ar- C_{0-6} alkyl, or Het- C_{0-6} alkyl (*Gribble, et al.*, p. 4, line 12); each R^5 independently is H, C_{1-6} alkyl, C_{2-6} alkenyl, Ar- C_{0-6} alkyl, or Het- C_{0-6} alkyl (*Gribble, et al.*, p. 4, lines 13-14); R^6 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl- C_{0-6} alkyl, Ar- C_{0-6} alkyl, or Het- C_{0-6} alkyl (*Gribble, et al.*, p. 4, lines 15-16); R' is H, C_{1-6} alkyl, C_{2-6} alkenyl, Ar- C_{0-6} alkyl, or Het- C_{0-6} alkyl (*Gribble, et al.*, p. 4, line 17); R'' C_{1-6} alkyl, Ar- C_{0-6} alkyl, Het- C_{0-6} alkyl, Ar- C_{2-6} alkenyl, or Het- C_{2-6} alkenyl (*Gribble, et al.*, p. 4, lines 18-19); X is O or S (*Gribble, et al.*, p. 4, line 20); n is 1, 2 or 3 (*Gribble, et al.*, p. 4, line 21).

The Difference Between the Prior Art and the Claims (MPEP §2141.02)

The difference between the prior art of *Gribble, et al.* and the instant invention is that the applicants are claiming various substituents (i.e. methyl) at the α -carbon position on the ketone bearing ring structure opposed to hydrogen. The elected species of the instant application possesses a methyl group at the α -carbon position.

Prima Facie Obviousness-The Rational and Motivation (MPEP §2142-2413)

In *In re Druey*, 319 F. 2d 237, 138 U.S.P.Q. 39 (C.C.P.A. 1963), it was well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. Replacing hydrogen with methyl usually does not result in a significant difference in biological activities. Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to substitute for instance, a methyl for hydrogen at the α -carbon position of the ketone bearing ring structure.

V. Objections

Claim Objection-Non Elected Subject Matter

Claims 1-14 are objected to as containing non-elected subject matter. To overcome this objection, Applicant should submit an amendment deleting the non-elected subject matter.

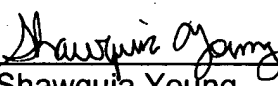
VI. Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shawquia Young whose telephone number is 571-272-9043. The examiner can normally be reached on 7:00 AM-3:30PM.

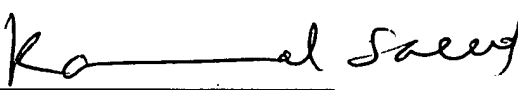

Art Unit: 1626

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


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4/27/06


 Joseph McKane
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